Age-specific serum anti-Müllerian hormone levels: estimates from a large population-based sample

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Key words: ANTI-MÜLLERIAN HORMONE, AGE-SPECIFIC, TEHRAN LIPID AND GLUCOSE STUDY (TLGS), REFERENCE VALUE, OVARIAN RESERVE

ABSTRACT

Objective Despite the wide use of anti-Müllerian hormone (AMH) measurement as a clinical marker for assessment of ovarian reserve, a population-based estimate for its reference values is not available. In this study, we have estimated age-specific AMH levels in a large sample of fertile women directly selected from a general population cohort.

Methods All women who were naturally fertile and aged 18–50 years with regular menstrual cycles were selected from the Tehran Lipid and Glucose Study cohort and their blood levels of AMH were measured. Centiles for AMH distribution were estimated according to the exponential–normal 3-parameter model. We repeated the analysis after including a subgroup of women aged 40–50 years who met all the eligibility criteria except having entered natural menopause after age 40 years ($n = 141$).

Results A total of 1015 women entered the study. The mean age was 36.7 years (standard deviation 7.5 years) and the mean body mass index was 27.0 kg/m^2 (standard deviation 4.6 kg/m^2). A non-linear decline of serum AMH concentration with age was observed. Age-specific AMH levels for the 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles were calculated. Results were reproduced after inclusion of 141 women aged 40–50 years who met all the eligibility criteria except having entered natural menopause after 40 years.

Conclusion In this study, we have presented a nomogram of age-specific estimates of anti-Müllerian hormone in a large sample of naturally fertile women within the general population. This could help clinicians in more accurate individual interpretation of serum AMH levels in healthy women.

INTRODUCTION

There is growing body of research suggesting anti-Müllerian hormone (AMH) as the best biomarker for determining ovarian reserve or prediction of age at menopause[1–4], as it accurately reflects the gradual age-related decline of reproductive capacity[5–7]. Several nomograms for AMH have been published[1,8–18], of which only a small number were in fertile women[1,8,9,13,16,17]. All existing literature used hospital-based samples which may not be suitable for the general population. Few studies had access to large samples and some were restricted by lack of a uniform, widely acceptable laboratory measurement kit for AMH, resulting in use of unreliable conversion factors within a single study[1,13].

In this study, we have estimated age-specific AMH levels in a large sample of fertile women directly selected from a general population cohort.

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MATERIALS AND METHODS

We used data from the Tehran Lipid and Glucose Study (TLGS). This is an ongoing, prospective, general population cohort from a geographically defined population of a district in Tehran initiated in 1998 to assess the prevalence and risk factors of non-communicable diseases. A total number of 15 005 people were selected through multistage cluster sampling and enrolled in the cohort after signing a written informed consent[19]. Subjects were physically examined and their demographic and reproductive characteristics as well as blood samples were collected. Blood samples were taken from the participants between 07.00 and 09.00 after 12 h overnight fasting. Samples were centrifuged within 30–45 min of collection and stored at -80°C. Questions about reproductive history included marital status, regularity of menstrual cycle, parity, history of infertility, and current and previous use of contraceptive methods.

We examined all women aged 18–50 years who were participants in the TLGS and selected those who met our eligibility criteria ($n = 1015$), which included having regular and predictable menstrual cycles at the initiation of the study, having proven natural fertility (at least one term pregnancy within 1 year after stopping contraception), and no history of endocrine disorders, hysterectomy, oophorectomy or any other kind of ovarian surgery. All eligible women had discontinued hormonal contraception for at least 3 months before entering the study. We excluded those with incomplete data or those for whom blood samples were not available.

The serum concentration of AMH at the time of recruitment was measured by the two-site enzyme immunoassay (EIA) method using the Gen II kit (Beckman Coulter, Inc., CA, USA) and the Sunrise ELISA reader (Tecan Co., Salzburg, Austria). All AMH measurements were performed simultaneously at the same laboratory. AMH Gen II controls A79766 were used at two levels of concentration to monitor accuracy of assay. The intra- and inter-assay coefficients of variation were 1.9% and 2.0%, respectively.

Table 1 Characteristics of the study population ($n = 1015$). Data are given as mean (standard deviation)

Age (years)	36.7 (7.5)
Parity	3.1 (1.6)
Abortion	0.4 (0.7)
Body mass index (kg/m^2)	27.0 (4.6)
Waist circumferences (cm)	85.3 (11.1)
Hip circumference (cm)	104.1 (8.8)
Systolic blood pressure (mmHg)	111.1 (13.4)
Diastolic blood pressure (mmHg)	74.8 (9.5)
Anti-Müllerian hormone (ng/ml)	
20–30 years	3.5 (2.3)
31–40 years	1.7 (1.4)
41–50 years	0.6 (0.8)

Statistical analysis

The relationship between AMH levels and the characteristics of the study subjects such as body mass index (BMI) and parity were explored using pair-wise Spearman's correlation and partial correlation coefficients. The normal-based methodology described in Altman and Chitty[20], and Royston and Wright[21],

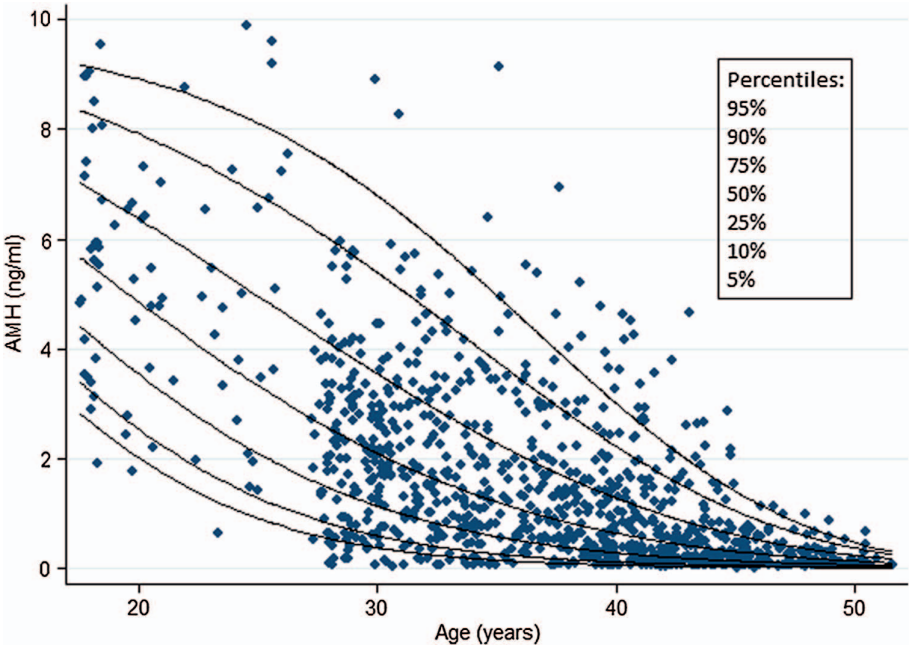

Figure 1 Anti-Müllerian hormone (AMH) percentiles in 1015 women

was used to estimate age-specific AMH percentiles. Fractional polynomial (FP) regression models were fitted separately to estimate the mean and standard deviation (SD) of the log AMH values as functions of age. The SD was modeled using the scaled absolute residuals from the estimated regression model for the mean. An FP of first degree with power 2 and a second-degree FP with powers (3, 3) were selected for mean and SD, respectively. The percentiles were obtained by combining these two regression models, using the assumption that the conditional distribution of log AMH values given age is normal. Percentile curves on the original scales (AMH nomogram) were obtained by taking the antilog of the calculated curves.

The normal plot of the *Z*-scores from the normal model described above showed that normality does not hold (p value for the Shapiro–Wilk test < 0.001). An exponential–normal (EN) 3-parameter model[22] provided a much improved fit, with a deviance 66.47 lower than the normal model ($p < 0.001$). The normal plot of the *Z*-scores from the EN model appears reasonably linear (p value for the Shapiro–Wilk test $= 0.16$), and 9.8% of the observations lie above the 90th percentile and 9.1% below the 10th percentile. The EN model was fitted by maximum likelihood using the STATA command xriml[23,24].

We repeated the analysis after including a subgroup of women aged 40–50 who met all the eligibility criteria except having entered natural menopause after age 40 years ($n = 141$). The date of their last cycle was recorded and an arbitrary value of 0.1 ng/ml was assumed as the serum concentration of AMH at that time. All statistical analyses were performed using STATA version 11 (Statacorp, TX, USA).

RESULTS

The demographic and reproductive characteristics of study participants are presented in Table 1. The mean age of the women was 36.7 years (SD = 7.5 years) and the mean BMI was 27.0 kg/m^2 (SD = 4.6 kg/m^2) with 34.3% and 40.9% of women having BMI values < 25 kg/m^2 and 25–29 kg/m^2, respectively; 24.8% were categorized as obese with BMI values > 30 kg/m^2. The mean AMH level was 1.65 ng/ml (SD = 1.81 ng/ml).

The correlation coefficient between AMH and BMI was $r = -0.15$ ($p < 0.001$). After adjustment for age, it changed to $r = 0.075$ ($p = 0.016$). There was a significant negative correlation between AMH levels and parity ($r = -0.39$; $p < 0.001$) and it became statistically non-significant after adjustment for age.

Figure 1 shows AMH values as a function of age and the estimated values of AMH for the 5th, 10th, 25th, 50th, 75th, 90th and 95th centiles in 1015 study participants, resulting from the EN model. The age-specific AMH values and their corresponding percentiles have been summarized in Table 2. Figure 2 and Table 3 show the AMH and age nomogram and their corresponding values after including the 141 menopausal women aged 40–50 ($n = 1156$). The results show a reduction in the 95th percentile cut-off value of AMH for women aged more than 40 years.

Table 2 Age-specific values of anti-Müllerian hormone and corresponding percentiles in the women ($n = 1015$)

Age (years)	Percentiles						
	5th	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
18	2.66	3.22	4.24	5.51	6.91	8.27	9.13
19	2.33	2.87	3.89	5.18	6.64	8.10	9.03
20	2.02	2.54	3.54	4.85	6.37	7.91	8.92
21	1.74	2.24	3.21	4.53	6.09	7.72	8.79
22	1.50	1.96	2.91	4.21	5.81	7.51	8.65
23	1.28	1.71	2.62	3.91	5.53	7.29	8.49
24	1.09	1.49	2.35	3.61	5.24	7.06	8.31
25	0.92	1.29	2.10	3.33	4.96	6.81	8.11
26	0.78	1.11	1.87	3.05	4.67	6.55	7.89
27	0.66	0.96	1.66	2.79	4.38	6.28	7.65
28	0.55	0.82	1.47	2.55	4.10	5.99	7.38
29	0.46	0.70	1.30	2.32	3.82	5.70	7.10
30	0.39	0.60	1.14	2.10	3.55	5.39	6.79
31	0.32	0.51	1.00	1.89	3.28	5.08	6.46
32	0.27	0.44	0.88	1.70	3.02	4.75	6.11
33	0.23	0.37	0.77	1.53	2.76	4.43	5.74
34	0.19	0.32	0.67	1.37	2.52	4.10	5.36
35	0.16	0.27	0.59	1.22	2.28	3.77	4.97
36	0.13	0.23	0.51	1.08	2.06	3.44	4.57
37	0.11	0.20	0.45	0.95	1.85	3.12	4.17
38	0.10	0.17	0.39	0.84	1.65	2.81	3.78
39	0.08	0.15	0.34	0.74	1.46	2.51	3.39
40	0.07	0.13	0.29	0.65	1.29	2.22	3.01
41	0.06	0.11	0.26	0.57	1.13	1.95	2.64
42	0.05	0.10	0.22	0.49	0.98	1.70	2.30
43	0.05	0.08	0.19	0.43	0.85	1.46	1.97
44	0.04	0.07	0.17	0.37	0.73	1.25	1.68
45	0.04	0.07	0.15	0.32	0.62	1.05	1.41
46	0.03	0.06	0.13	0.27	0.52	0.88	1.17
47	0.03	0.05	0.11	0.23	0.44	0.72	0.95
48	0.03	0.05	0.10	0.20	0.36	0.59	0.77
49	0.03	0.04	0.09	0.17	0.30	0.47	0.61
50	0.03	0.04	0.08	0.14	0.25	0.38	0.48
51	0.02	0.04	0.07	0.12	0.20	0.29	0.37
52	0.02	0.04	0.06	0.10	0.16	0.23	0.28
53	0.02	0.03	0.05	0.09	0.13	0.17	0.21
54	0.02	0.03	0.05	0.07	0.10	0.13	0.15
55	0.03	0.03	0.04	0.06	0.08	0.10	0.11

DISCUSSION

Our study reports age-specific serum AMH levels for a large sample of naturally fertile women that to the best of our knowledge for the first time were taken directly from a general population cohort.

Several nomograms for AMH have been published[1,9–18] so far, but the majority of these nomograms are based on measurements performed in infertile women[10–12,14,15,18]. The results from these studies could not be generalized to a normal population as their ovarian aging is highly influenced by their associated conditions such as polycystic ovary

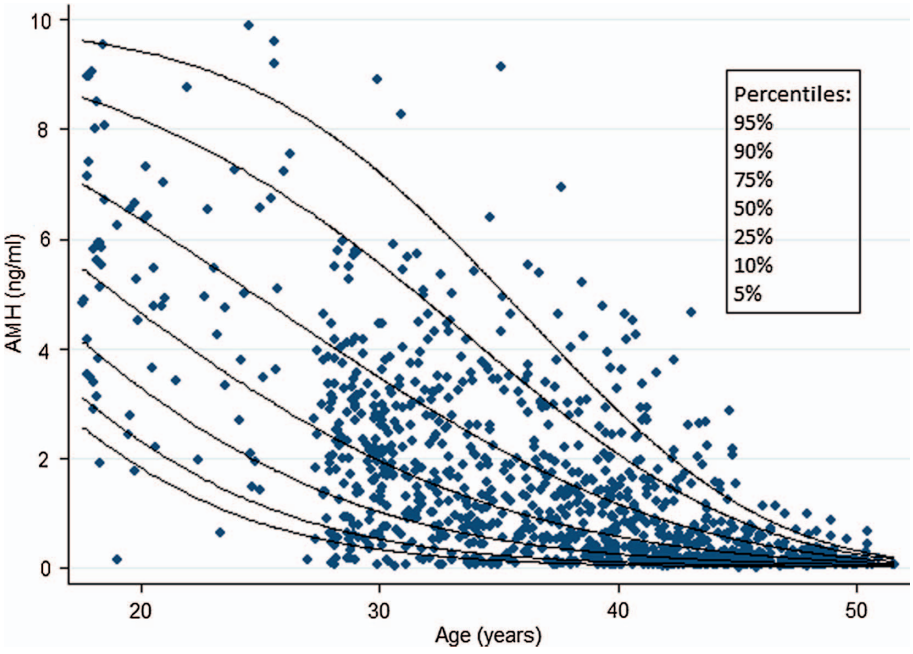

Figure 2 Anti-Müllerian hormone (AMH) percentiles in 1156 women

syndrome[25], endometriosis[26] and ovarian surgeries[27]. There are a few hospital-based studies reporting AMH nomograms for healthy women[1,8,9,13,17]. However, they may not fully represent the general population and all except one of them did not have access to a large sample; this large study was conducted among 1298 Korean women visiting hospitals but the reasons for their visits have not been reported[13]. Furthermore, AMH nomograms were obtained via a mixture of various AMH lab kits[1] and unreliable conversion factors[28] may not be sufficiently reliable. The current study, however, uses a large sample of healthy fertile women from the community to make the AMH nomogram.

Compared to the available estimates for age-specific AMH levels for healthy fertile women[8], our results have fewer fluctuations. This could be due to its large sample size (having adequate numbers of women in various age groups) and clear eligibility criterion of 'proven fertility'. Our AMH estimates are somewhat lower than those reported by studies without 'proven fertility' as one of their essential inclusion criteria[9,13]. This could be because their results may have been influenced by the AMH levels of those with hidden fertility problems.

Several statistical models have been introduced to present the relationship between age and AMH. In agreement with most data available[1,8,11,15], our study shows a non-linear AMH decline with age. Several non-linear models have been presented and their suitability assessed by taking into account their goodness of fit (r^2 values) as well as their simplicity. The quadratic model was found to be the most appropriate model by many researchers, given its comparable r^2 values and ease of interpretation[8,11,15]. However, we found that the EN 3-parameter model provided a decent fit; the normal plot of the *Z*-scores from our model appears reasonably linear and about 10% of the observations lie above the 90th percentile and about 10% below the 10th percentile.

We believe that reaching menopause after age 40 years is considered a physiologic reproductive event[29–31], while in our original sample ($n = 1015$) we had excluded all women who had entered menopause regardless of their age. The cross-section of women who had entered our study in this way did not therefore fully reflect the study population. As they reached older age, more women with longer reproductive life spans remained in our sample and the representativeness of the sample further deteriorated. In other words, not all healthy fertile women aged 40–50 had an equal chance of participating in the sample. To overcome this problem, we included women who had reached menopause after 40 years of age given that they met other eligibility criteria ($n = 141$). However, as we could not measure their AMH level at the time of menopause, an arbitrary value of 0.1 ng/ml, based on literature[32], was assigned to them; this we believe provided estimates of AMH percentiles that better reflect the true AMH range in the general population of women. We observed a downward shift in the percentile curves, as we expected, providing more realistic values of AMH particularly for the older age groups in our study population.

We found that AMH levels and BMI were negatively correlated, which is similar to the findings of other studies[9,33–35] and may be partly explained by the fact that aging women tend to have a higher BMI. Adjustment for age changed the correlation coefficient between AMH and BMI from $r = 0.15$ ($p < 0.001$) to $r = 0.075$ ($p = 0.016$) which supports the above assertion. We found no significant relationship between the number of pregnancies and AMH levels after adjustment for

Table 3 Age-specific values of anti-Müllerian hormone and corresponding percentiles in the women ($n = 1156$)

Age (years)	Percentiles						
	5th	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
18	2.43	2.95	3.97	5.31	6.88	8.51	9.59
19	2.11	2.62	3.62	4.98	6.62	8.35	9.51
20	1.83	2.31	3.29	4.65	6.35	8.18	9.42
21	1.58	2.03	2.98	4.34	6.07	7.99	9.31
22	1.35	1.77	2.68	4.03	5.79	7.78	9.19
23	1.15	1.54	2.41	3.72	5.50	7.56	9.04
24	0.98	1.34	2.15	3.43	5.21	7.33	8.86
25	0.83	1.16	1.92	3.15	4.92	7.07	8.66
26	0.70	1.00	1.70	2.89	4.63	6.80	8.43
27	0.59	0.86	1.51	2.64	4.34	6.51	8.17
28	0.50	0.73	1.33	2.40	4.05	6.20	7.88
29	0.42	0.63	1.17	2.17	3.76	5.88	7.56
30	0.35	0.54	1.03	1.96	3.48	5.55	7.21
31	0.29	0.46	0.91	1.76	3.20	5.20	6.83
32	0.25	0.39	0.79	1.58	2.93	4.85	6.43
33	0.21	0.34	0.69	1.41	2.67	4.49	6.00
34	0.18	0.29	0.61	1.26	2.42	4.12	5.56
35	0.15	0.25	0.53	1.12	2.18	3.76	5.10
36	0.13	0.21	0.46	0.99	1.95	3.40	4.64
37	0.11	0.18	0.40	0.87	1.74	3.05	4.18
38	0.09	0.16	0.35	0.77	1.54	2.71	3.73
39	0.08	0.14	0.31	0.67	1.35	2.39	3.29
40	0.07	0.12	0.27	0.58	1.18	2.08	2.86
41	0.06	0.11	0.23	0.51	1.02	1.79	2.46
42	0.06	0.09	0.20	0.44	0.87	1.53	2.09
43	0.05	0.08	0.18	0.38	0.74	1.29	1.75
44	0.05	0.07	0.16	0.33	0.63	1.07	1.45
45	0.04	0.07	0.14	0.28	0.53	0.88	1.18
46	0.04	0.06	0.12	0.24	0.44	0.72	0.94
47	0.04	0.06	0.11	0.20	0.36	0.57	0.74
48	0.04	0.05	0.10	0.17	0.29	0.45	0.57
49	0.03	0.05	0.09	0.15	0.24	0.35	0.44
50	0.03	0.05	0.08	0.12	0.19	0.27	0.33
51	0.03	0.05	0.07	0.10	0.15	0.20	0.24
52	0.04	0.04	0.06	0.09	0.12	0.15	0.17
53	0.04	0.04	0.06	0.07	0.09	0.11	0.12
54	0.04	0.04	0.05	0.06	0.07	0.08	0.08
55	0.04	0.04	0.05	0.05	0.05	0.05	0.06

age. Therefore, as shown by other studies[9,36], it seems that reproductive outcomes of fertile women are not related to their individual age-specific AMH levels.

This is the first study reporting an AMH nomogram among a general Iranian population. There is some research suggesting that ovarian aging or AMH levels may be influenced by race and ethnicity[37,38] and disparity in reproductive aging among Asian subpopulations has been reported[39]. However, the results of the Study of Women's Health Across the Nations (SWAN) demonstrated no difference in menopausal age among various racial/ethnic groups after controlling for sociodemographic and lifestyle factors[40]. Furthermore, it has been shown that European and Iranian women share age at natural menopause-associated genetic variants[41]. Therefore, we believe that the estimates we have provided are reasonably applicable to all women.

There are suggestions that AMH may be unstable under some storage or assay conditions, particularly when the Gen II kit[42] is used for assays. We believe this is not a problem in our study considering that blood samples taken as part of the TLGS study were centrifuged within 30–45 min of collection and stored at −80°C. The amount of intra-assay variability in our data is likely to be minimal because all the laboratory measurements were performed simultaneously at the same laboratory by the same person. Another challenge is the interpretation of values obtained by various AMH kits[28]. Despite an excellent correlation between the new Gen II kit and both the Diagnostic Systems Lab (DSL) and Immunotech (IOT) systems[43,44], however, there is no universal conversion factor for converting values obtained by the Gen II kit to the other two mentioned. Therefore we do not recommend adapting our age-specific AMH cut-offs based on the Gen II assay to older ones by direct conversion.

In this study, we have presented a nomogram of age-specific estimates of anti-Müllerian hormone in a large sample of naturally fertile women within the general population. This could help clinicians in more accurate individual interpretation of serum anti-Müllerian hormone levels in healthy women.

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